AMENDMENTS TO THE DRAWINGS

The 4 drawing sheets attached in connection with the above-identified application containing figures 4, 5, 7, and 8 are being presented as a new drawing sheets to be substituted for the previously submitted drawing sheets. No change is being made, as the replacement drawings are presented in better quality.

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of the Claims

Claims 1-60 were previously cancelled. Claim 86 has been amended to correct the alphabetical denotation of each step of the claimed method and to recite the specific protease. Exemplary support can be found in the original claim 86 and in the specification, at page 26, lines 29-31. Claims 87 and 88, which depend from claim 86, have been amended accordingly to reflect the corresponding steps and the protease.

Claims 123-127 have been added, with exemplary support in the specification listed in the table below:

Claim	Exemplary Support
123	page 18, 2nd paragraph; page 67, lines 27-29
124	page 18, lines 8-9
125	Example 8, page 67, line 27 to page 68, line 7
126	Example 8, page 67, line 27 to page 68, line 7
127	Example 8, page 67, line 27 to page 68, line 7

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 61-127 will be pending, with claims 61-85 and 89-122 withdrawn.

II. Priority Claim

Applicants submit herewith a certified copy of the English translation of priority application No. DE 10211063.8, filed on March 13, 2002. Accordingly, the present application benefit from the priority date of March 13, 2002. Applicants respectfully request the Examiner acknowledge the priority claim in the next Office Action.

III. Objection to the Drawings

Figures 24 and 25 are objected for alleged lack of sequence identifiers. Nevertheless, figure 24 depicts the diagrammatic representation of the plasmid constructs, while figure 25 depicts a flowchart of the protein interaction-regulated system. No sequence is identified in the figures at issue that require a sequence identifier. Applicants respectfully request the Examiner clarify the deficiency or withdraw the objection to figures 24 and 25.

Figures 4, 5, 7, and 8 are objected for their poor quality. Replacement drawings for figures 4, 5, 7, and 8 are concurrently submitted to obviate the basis for the objection.

IV. Objection to the Abstract

A new abstract in compliance with MPEP 608.01(b) is appended to the end of this response to replace the previously submitted abstract. Accordingly, withdrawal of the objection to the abstract is warranted.

V. Objection to the Specification

The specification is objected to for alleged lack of a paragraph cross-referencing the related applications. A paragraph has been inserted in the beginning of the specification, making reference to the corresponding PCT application and the priority application.

The specification is also objected for alleged lack of sequence identifiers. The specification has been amended accordingly to insert the SEQ ID NOs.

Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

VI. Objection to the Claims

The claims set is objected to for failing to begin with "We claim" or "The claims are." Applicants respectfully request "We claim" be inserted in the beginning of the replacement

list of claims accompanying this response. Accordingly, the stated basis for the objection should be obviated.

VII. Rejection of Claims under 35 U.S.C. § 112, Second Paragraph

Claims 86-88 are rejected for allegedly being indefinite. Specifically, the Examiner rejected the claims for improper alphabetical denotation of each method step. Accordingly, the claims have been amended, with the steps denoted from a) to c). Therefore, the rejection should be withdrawn.

VIII. Rejection of Claims under 35 U.S.C. § 112, First Paragraph

Claims 86-88 are rejected for alleged lack of enablement and written description. Specifically, the Examiner contends that the specification does not support or enable "a method of detecting protein interaction in a cell using a first and second fusion protein [sic] comprising domains of any protease and any reporter" (Office Action, page 5, second paragraph). Applicants respectfully traverse the grounds of the rejection.

Claims 86-88 have been amended to recite the specific protease, TEV protease. The specification clearly describes that the activity of a TEV protease can be reconstituted when TEV fragments are being brought in close proximity to each other by protein-protein interactions. *See, e.g.* Example 8. The specification also discloses the reporter proteins to be used for the claimed method. The exemplary reporter proteins are GFP and luciferase (page 33, lines 19-31). Since the cleavage site of the TEV protease is well known, one skilled in the art is enabled to provide reporter proteins that can be inactivated or activated by cleavage with the TEV protease. Claims 87 and 88 further recite inactivating or activating proteins by proteolysis, such as by adding specific cleavage sites. Accordingly, the claimed methods are fully supported and enabled by the specification. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IX. Rejection of Claims under 35 U.S.C. § 103 (a)

A. Michnick, Ghelis and Carmel

Claims 86-88 are rejected for alleged obviousness over Michnick *et al.* (*Methods in Enzymology*, 328: 208-230, 2000) in view of Ghelis *et al.* (*Biochemical and Biophysical Research Communications*, 84: 31-36, 1978) and further in view of Carmel *et al.* (*FEBS Letters*, 30: 11-14, 1973). Applicants respectfully traverse the rejection.

The claimed invention, as recited in claim 86, relates to detecting and analyzing protein interactions in a cell by a protease-dependent reporting system, which comprises (i) a first fusion protein and a part of the TEV protease, (ii) a second fusion protein and another part of the TEV protease; and (iii) a reporter protein whose reporter activity can be activated or inactivated by proteolysis.

By contrast, the primary Michnick reference describes that a first protein is fused to a fragment of an enzyme, and a second protein is fused to another fragment of the enzyme. Interaction of the first protein and the second protein results in reassembly of the enzyme, which catalyzes the conversion of a substrate into a product.

The cited art is deficient in teaching or suggesting the claimed invention in several aspects, none of which but one is acknowledged by the Examiner: (A) As the Examiner admits, Michnick does not teach that the enzyme is a protease, let alone the TEV protease; (B) Michnick does not teach a reporter protein prescribed by claim 86, because a substrate is quite distinguished from a reporter protein; (C) Michnick does not teach the co-expression of a part of a TEV protease and a reporter protein; (D) Michnick does not teach that the reporter activity can be activated or inactivated by proteolysis; and therefore, it is not surprising that (E) Michnick does not teach step c) of claim 86, activation of the proteolysis-activatable or inactivation of the proteolysis-inactivatable reporter protein by the reconstituted functional protease.

The Examiner turns to the secondary references, Ghelis and Carmel, in an attempt to bridge the noticeable gap between Michnick and the claimed invention. Nevertheless, Ghelis and Carmel fail to remedy the deficiency because neither teaches activation or inactivation of a reporter protein due to proteolytic activity by the TEV protease.

The Examiner's rationale is that Gheli teaches folding and mixing the domains of elastase generates 2% activity, and therefore it would be obvious to use elastase for the claimed method. First of all, Gheli does not even relate to the detection of protein-protein interactions or to reconstitution of a protease *in vivo* to activate a reporter protein. Second, similar to the primary reference, Gheli fails to mention the TEV protease. Third, contrary to the Examiner's contention, one skilled in the art would not have been motivated to combine the teaching of Gheli with that of Michnick, because the activity of regenerated elastase is so low, only 2% of the native form.

The Examiner further asserts that "since mere mixing of the two domains of elastase regenerates only 2% of the activity, binding of the two fusion proteins would be expected to raise the elastase activity above this low level." There is no suggestion whatsoever in the cited reference to increase the activity of regenerated elastase by binding of the fusion proteins. Instead, Gheli attributes the weak activity to "an incomplete conformational readjustment of the domains upon complementation." Therefore, the stated rationale for rejection is based on nothing else but impermissible hindsight.

Accordingly, the Examiner failed to establish a *prime facie* case of obviousness for lack of motivation to combine the references and for improper hindsight.

The Examiner further relies on Carmel for the alleged teaching of detecting protease activity using a reporter. Carmel describes that the activity of a protease can be detected by cleavage of substrates with fluorescent donor and acceptor chromophores. Therefore, the substrates disclosed by Carmel are not the same as the reporter proteins used in the claimed method.

Applicants point out that the Examiner explicitly admits in the next section of the Office Action that "neither Michnick et al. nor Carmel et al., or the combination thereof, teach adapting the method of Michnick et al to use domains of the TEV protease to detect protein-protein interaction" (Action, page 10, lines 12-14). Since Gheli does not even mention TEV protease, the combined teachings of Michnick, Gheli and Carmel clearly do not

render the claimed invention obvious. Therefore, withdrawal of the rejection is respectfully requested.

B. Michnick, Bazan, Carmel, Stevens and Sawyer

Claims 86-88 are rejected for alleged obviousness over Michnick in view of Bazan *et al.* (*Proc. Natl. Acad. Sci. USA*, 85: 7872-7876, 1988) and further in view of Carmel, as evidenced by Stevens (*Structure* 8: R177-R185, 2000) and Sawyer *et al.* (*J. Mol. Biol.* 118: 137-208, 1978). Applicants respectfully traverse the rejection.

Applicants discuss the publications by Michnick and by Carmel in the foregoing paragraphs. The Examiner acknowledges that the combined teachings of Michnick and Carmel do not suggest the use of TEV protease. As a remedy, the Examiner makes reference to Bazan at page 7875, paragraph 2 and figure 3 for the alleged teaching that "like elastase, the structure of TEV protease has twin β-barrel trypsin-like folds" (Action, page 10, lines 14-15). Contrary to the Examienr's assertion, the cited portion of Bazan does not teach any structural similarities between elastase and TEV protease. More importantly, the Examiner's rationale must fail because one skilled in the art would not have been motivated to use TEV protease in the claimed method merely because of the structural similarity between elastase and TEV protease.

To provide a motivation, the Examiner cites Stevens as alleged evidence that TEV protease has very high substrate specificity. Even so, the rejection is based on faulty ground because there is no suggestion in any cited reference that a protease with structural similarity to elastase and with high substrate specificity is desired, thereby leading one skilled in the art to the TEV protease in the claimed method. Once again, the Examiner can only base his rejection on 20/20 hindsight.

Because the Examiner fails to establish a *prime facie* case of obviousness, withdrawal of the rejection is warranted.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 20 September 2007

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